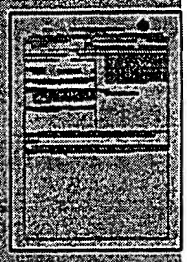

WO9902165A1: PROSTAGLANDIN DERIVATIVES DEVOID OF SIDE-EFFECTS FOR THE TREATMENT OF GLAUCOMA

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Issued/Filed Dates: **Jan. 21, 1999** / July 10, 1998

Application Number: **WO1998SE0001368**

IPC Class: **A61K 031/557;**

Priority Number(s): July 11, 1997 **SE1997000027064**

Designated Countries: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, **European patent:** AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, **OAPI patent:** BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG, **ARIPO patent:** GH, GM, KE, LS, MW, SD, SZ, UG, ZW, **Eurasian patent:** AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

Abstract: A new method and compositions for the treatment of glaucoma and ocular hypertension are described. The method is based on the usage of EP1 prostanoidreceptor agonists which effectively reduce the intraocular pressure but have no, or reduced effect on iris pigmentation. The prostaglandin analogue which is an EP1 selective agonist is applied topically on the eye.
[Show "fr" Abstract]

Attorney, Agent, or Firm: **SVANSTRÖM, Pär;**

Foreign References: **none**

(No patents reference this one)

[1] **Premium Data:** Using the premium data links may invoke a charge to your account.

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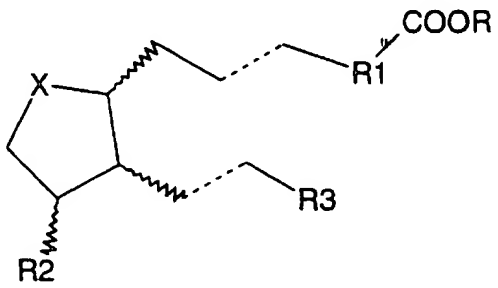
CLAIMS

1. A composition for the treatment of glaucoma and ocular hypertension comprising a therapeutically active and physiologically acceptable amount of a prostaglandin analogue which is a selective agonist for EP_1 prostanoid receptors, or a pharmaceutically acceptable salt or ester thereof.

2. The composition according to claim 1, wherein the prostaglandin analogue is derived from PGF or PGE type prostaglandins.

3. The composition according to claim 1 or 2, wherein the prostaglandin analogue is a compound of the general formula:



wherein:

the wavy bonds represent the α or β configuration, and the dashed bonds represent a single bond, a triple bond or a double bond in the cis or trans configuration;

R is hydrogen, saturated or unsaturated alkyl, preferably C_{1-10} alkyl, cycloalkyl, preferably C_{3-8} cycloalkyl, aryl, arylalkyl, preferably aryl-C_{2-5} alkyl, or heteroaryl;

R1 is a saturated or unsaturated alkyl group having 2-5 carbon atoms, optionally interrupted by a heteroatoms selected from oxygen, sulfur and nitrogen, cycloalkyl, preferably C_{3-7} cycloalkyl, cycloalkenyl, preferably C_{3-7} cycloalkenyl, aryl or heteroaryl;

X is C-OH or C=O;

R2 is hydrogen, hydroxy, methyl, ethyl, methoxy or OCOR4, where R4 is a straight or branched chain saturated or unsaturated alkyl group, preferably C_{1-10} alkyl, especially C_{1-6} alkyl, or a cycloalkyl, preferably C_{3-8} cycloalkyl, or aryl group;

R3 is a straight or branched chain saturated or unsaturated alkyl group, preferably having 3-8 carbon atoms, especially 3-5 carbon atoms, optionally interrupted by one or more heteroatoms selected from oxygen, sulfur and nitrogen, each carbon atom optionally being substituted with a substituent selected from C_{1-5} alkyl, hydroxy and carbonyl groups, hydroxy and carbonyl preferentially being attached to carbon 15 of the prostaglandin structure, and said alkyl group optionally containing a cycloalkyl, preferably C_{3-8} cycloalkyl, aryl or heteroaryl group, which may be mono- or independently multi-substituted with C_{1-3} alkyl, C_{1-3} alkoxy, hydroxy, nitro, trifluoromethyl or halogen;
or a pharmaceutically acceptable salt or ester thereof.

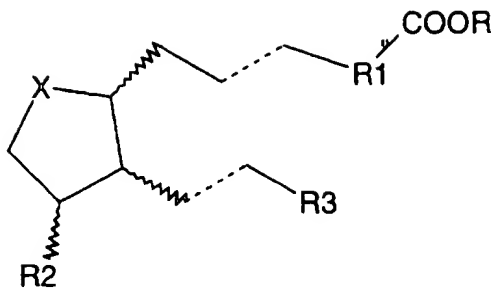
4. The composition according to claim 1, 2 or 3, wherein the prostaglandin analogue is 15(R,S)-16,16-trimethylene-PGE_2 or an alkyl ester thereof.

5. The composition according to claim 1, 2 or 3 wherein the prostaglandin analogue is 13,14-dihydro-17-(3-fluorophenyl)-18,19,20-trinor-PGE_2 or an alkyl ester thereof.

6. A method of treating glaucoma or ocular hypertension in a subject's eye, which method comprises contacting the surface of the eye with an effective intraocular pressure reducing amount of a therapeutically active and physiologically acceptable prostaglandin analogue which is a selective agonist for EP_1 prostanoid receptors, or a pharmaceutically acceptable salt or ester thereof.

7. The method according to claim 6, wherein the prostaglandin analogue is derived from PGF or PGE prostaglandins.

8. The method according to claim 6 or 7, wherein the prostaglandin analogue is a compound of the general formula:



wherein:

the wavy bonds represent the α or β configuration, and the dashed bonds represent a single bond, a triple bond or a double bond in the cis or trans configuration;

R is hydrogen, saturated or unsaturated alkyl, preferably C_{1-10} alkyl, cycloalkyl, preferably C_{3-8} cycloalkyl, aryl, arylalkyl, preferably aryl-C_{2-5} alkyl, or heteroaryl;

R1 is a saturated or unsaturated alkyl group having 2-5 carbon atoms, optionally interrupted by a heteroatoms selected from oxygen, sulfur and nitrogen, cycloalkyl, preferably C_{3-7} cycloalkyl, cycloalkenyl, preferably C_{3-7} cycloalkenyl, aryl or heteroaryl;

X is C-OH or C=O;

R2 is hydrogen, hydroxy, methyl, ethyl, methoxy or OCOR4, where R4 is a straight or branched chain saturated or unsaturated alkyl group, preferably C_{1-10} alkyl, especially C_{1-6} alkyl, or a cycloalkyl, preferably C_{3-8} cycloalkyl, or aryl group;

R3 is a straight or branched chain saturated or unsaturated alkyl group, preferably having 3-8 carbon atoms, especially 3-5 carbon atoms, optionally interrupted by one or more heteroatoms selected from oxygen, sulfur and nitrogen, each carbon atom optionally being substituted with a substituent selected from C_{1-5} alkyl, hydroxy and carbonyl groups, hydroxy and carbonyl preferentially being attached to carbon 15 of the prostaglandin structure, and said alkyl group optionally containing a cycloalkyl, preferably C_{3-8} cycloalkyl, aryl or heteroaryl group, which may be mono- or independently multi-substituted with C_{1-3} alkyl, C_{1-3} alkoxy, hydroxy, nitro, trifluoromethyl or halogen;

or a pharmaceutically acceptable salt or ester thereof.

9. The composition according to claim 6, 7 or 8, wherein the prostaglandin analogue is 15(R,S)-16,16-trimethylene-PGE_2 or an alkyl ester thereof.

10. The composition according to claim 6, 7 or 8 wherein the prostaglandin analogue is 13,14-dihydro-17-(3-fluorophenyl)-18,19,20-trinor-PGE_2 or an alkyl ester thereof.

11. The method according to any one of claims 6-10, wherein a therapeutically active and physiologically acceptable composition containing said prostaglandin analogue is administered topically on the eye 1-3 times daily.

12. Use of a prostaglandin analogue which is a selective agonist for EP_1 prostanoid receptors as defined in any one of claims 1 to 4 for the preparation of a medicament for treatment of glaucoma and ocular hypertension.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/01368

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/557
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9408585 A1 (ALCON LABORATORIES, INC.), 28 April 1994 (28.04.94) --	1-3,12
X	Journal of Lipid Mediators, Volume 6, 1993, David F. Woodward et al, "Intraocular pressure effects of selective prostanoid receptor agonists involve different receptor subtypes according to radioligand binding studies" page 545 - page 553 --	1-3,12
A	The Journal of Biological Chemistry, Volume 268, No 27, Sept 1993, Akiko Watabe et al, "Cloning and Expression of cDNA for a Mouse EP1 Subtype of Prostaglandin E Receptor", page 20175 - page 20178 --	12

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 October 1998	01 -11- 1998
Name and mailing address of the ISA/ Swedish Patent Office	Authorized officer

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/01368

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Natural product reports, Volume 7, No 5, 1990, D. E. Bays et al, "Inhibitors of Gastric Acid Sectretion", page 409 - page 445, see page 436	12
	--	
X	US 4132738 A (HAROLD C. KLUENDER ET AL), 2 January 1979 (02.01.79)	1-4
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/01368

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 6-8,11
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1.

2. [X] Claims Nos.: 12
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The expression "a selective agonist for EP1 prostanoid receptors" in claim 12 is indefinite. According to PCT Article 6, the claims shall be clear and concise. Claim 12 has therefore not been fully searched.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

27/07/98

International application No.
PCT/SE 98/01368

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9408585 A1	28/04/94	AT 153855 T	15/06/97
		AU 674038 B	05/12/96
		AU 5328694 A	09/05/94
		DE 69311361 D,T	08/01/98
		EP 0664707 A,B	02/08/95
		ES 2105333 T	16/10/97
		JP 8502485 T	19/03/96
		US 5480900 A	02/01/96
		US 5605922 A	25/02/97
US 4132738 A	02/01/79	AU 515772 B	30/04/81
		AU 4449379 A	30/08/79
		CA 1191132 A	30/07/85
		DE 2902699 A,B,C	30/08/79
		FR 2430403 A,B	01/02/80
		FR 2473509 A,B	17/07/81
		GB 2014989 A,B	05/09/79
		GB 2099814 A,B	15/12/82
		JP 1194012 C	12/03/84
		JP 54115351 A	07/09/79
		JP 58026910 B	06/06/83
		SE 441673 B,C	28/10/85
		SE 445109 B,C	02/06/86
		SE 453830 B,C	07/03/88
		SE 453990 B,C	21/03/88
		SE 7813385 A	24/08/79
		SE 8303910 A	08/07/83
		SE 8303911 A	08/07/83
		SE 8303912 A	08/07/83
		US 4275224 A	23/06/81
		US 4331688 A	25/05/82
		US 4415592 A	15/11/83
		US 4742080 A	03/05/88
		US 4833157 A	23/05/89

CLAIMS

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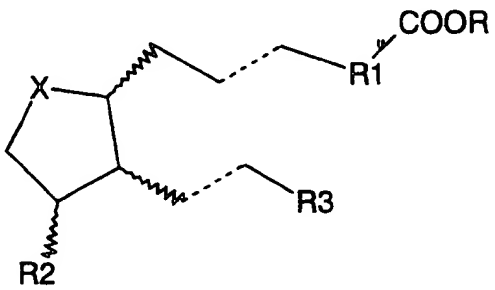
2. The composition according to claim 1, wherein the prostaglandin analogue is derived from PGF or PGE type prostaglandins.

3. The composition according to claim 1 or 2, wherein the prostaglandin analogue is a compound of the general formula:



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